REMARKS

Claims 1-37 and 45-60 remain pending in the application. Claims 1, 16, 18-20, 23, 24, 32, 37, 45, 49-52 and 58-60 have been amended herein. Claim 38 has been cancelled. The amendments have been effected primarily to address various issues raised by the Examiner under 35 USC §112, paragraphs 1 and 2, to correct inadvertent errors and as a consequence of the cancellation of claim 38. The amendments herein conform with the requirements for such made after final rejection; they reduce the issues for appeal and raise no new issues. Furthermore, no new claims have been added, while one previously pending claim has been cancelled. Entry and consideration of the amendments herein are respectfully requested.

Applicants acknowledge the Examiner's withdrawal of a number of objections and rejections and the recognition that the application is now in sequence compliance.

There apparently remains some confusion with respect to the Swedish priority application. In Paper No. 6, the Examiner acknowledged Applicants' claim for foreign priority and indicated that a certified copy of said document was in the application file. However, the Examiner since then has continued to request a certified copy of an English translation of said document. It is a fact that the priority application was filed in the Swedish Patent Office in the English language and, thus, the document already acknowledged

by the Examiner to be in the file should be all that is required. This notwithstanding, to make certain there are no questions in this regard, Applicants provide herewith a second certified copy of the priority document, the cover page indicating that said document is a true copy as originally filed and that it was filed in English.

Claims 50-52 remain objected to as being improperly multiply dependent. Claim 50 has been amended herein so that it no longer depends from claim 49, thus rendering moot the rejection of all three claims.

A number of the claims (it is not clear, from the way the Examiner has set it out, all of the claims that are asserted to fall under this rejection) have been rejected as being nonenabled. The Examiner asserts that the specification "does not reasonably provide enablement for vaccines comprising any protein from any source or any Helicobacter protein from any species or any fragment of any Helicobacter protein."

The Examiner appears to have lost sight of the fact that the invention is not directed to vaccines per se. As is clearly set forth in the instant specification, the object of the invention is to provide a means of delivering a water-insoluble antigen in a W/O emulsion such that the antigen can, despite its insolubility in water, stimulate the production of antibodies which could be effective in the treatment of a particular disease or infection. This represents a

significant improvement over what was previously known and possible in the field. Prior to the present invention, only water-soluble antigens were considered in techniques involving formation of W/O emulsions, since in such a technique the antigen must be solubilized in the aqueous (W) phase (see, e.g., page 5, lines 15-25 of the instant specification).

The specification provides numerous examples of the type of delivery system claimed in the application and further provides data showing the effectiveness of such a W/O emulsion delivery system in affording generation of antibodies from a water-insoluble antigen. As would be clear to one of skill in the art reading the application, the techniques claimed herein can potentially be applied to any water-insoluble antigen. Again, it is important to emphasize that Applicants are not claiming per se vaccines raised against all water-insoluble antigens; they are claiming a method by which such antigens can be delivered via a W/O emulsion with the potential for generating an immune response. Before Applicants' invention, no success could even remotely be anticipated in delivering such an antigen in a W/O emulsion system. Accordingly, the present scope of the claims is perfectly enabled, and the rejection should be withdrawn.

The rejection of claim 1 under 35 USC §102(a) as being anticipated by Lee et al. has been maintained. The submission herewith of a second certified copy of the Swedish priority document renders moot this rejection.

The Examiner has maintained the rejection of claim 1 under 35 USC §102(b) as being anticipated by Goldstein et al. and has added claims 26, 27 and 36 to this rejection. In the first place, it is unclear to Applicants how claim 36 found its way into this rejection. In any event, as the basis for this rejection the Examiner asserts that the subject matter recited in the claims in question is anticipated by Goldstein, since claim 1 does not expressly say that the recited steps are to be carried out sequentially; this is certainly an inappropriate ground of rejection. It is inherent in the setting out of steps that the steps are to be carried out in the order given, unless some language is added to specify otherwise, e.g., that order is not important.

The Examiner goes on to assert that the phrase "protein fragment" in the instant claims could encompass a single amino acid, as disclosed in the Goldstein reference. In the first place, Applicants note that the Examiner has had to bring in a completely different reference, that of Murray, as the basis for this assertion. Thus, the Examiner is in effect admitting that the two references must be combined; accordingly, even if the combination could be said to teach the instant invention (which it cannot), is certainly cannot be said that the cited Goldstein reference anticipates each and every aspect of the instant invention.

Regardless, the Examiner's assertion that the phrase "protein fragment" could encompass a single amino acid is

inappropriate in the context of the present invention. One of skill in the art would certainly recognize that the instantly recited "*Helicobacter* protein fragment" must be a portion of the intact protein that is recognizable as being derived from said intact protein. The test of patentability is what one of skill in the art might glean from the disclosure, not a unique interpretation made by the Examiner.

As another basis for the rejection, the Examiner asserts that the instantly claimed method "only recites a single step, while the method exemplified in the instant specification administered the composition three times;" again, the Examiner appears to have lost sight of the purport of the instant invention. The Examiner is reminded that, in the claims in question, Applicants are not claiming a method of immunizing; they are claiming a method for producing a delivery system. Thus, in the claims rejected by the Examiner, the number of times the composition containing the water-insoluble antigen has to be administered is clearly not even a part of the invention to be claimed.

Applicants note with great interest that the Examiner has indicated that claims 17 and 18 merely stand objected to as being dependent on a rejected base claim; the Examiner has indicated that they would be allowable if rewritten in independent form. As the Examiner recognizes, these two claims are further limited from the base claim only in reciting a chaotropic agent. In other words, the Examiner's

stance with respect to claims 17 and 18 is effectively an acknowledgment that the allegation of nonablement of claim 1 and claims dependent therefrom is without merit.

The rejection of claims 1-3, 6, 7, 9, 11-14, 38 and 49 under 35 USC §102(b) as being anticipated by U.S. Patent No. 4,610,868 to Fountain et al. has been maintained. The Examiner cites Fountain passages which allegedly disclose all of the features of the present invention. However, in the first place, Applicants wish to remind the Examiner that the claims under rejection are not directed to compositions per se but to processes for preparing compositions and, in one case, the compositions obtained by using the processes. Thus, the comparison of the chemical components of the instant invention with those disclosed by Fountain is not the last word in determining patentability of the instantly claimed subject matter over the cited reference. It is not just the components, then, but the way in which they are used, i.e., the steps in the claimed process that distinguish over the cited disclosure.

The Examiner has not commented on Applicants' previous arguments, by providing, for example, any asserted fallacies therein. For one, Applicants pointed out then, and still maintain, that the claims cited in this rejection recite that the "globular" structures of Fountain are already formed by agitation of the phases prior to removal of solvent, whereas in the present method (see step (b) of claim 1), the particles

are formed by the dispersion of the emulsion and with the removal of the solvent. Such considerations are equally or more relevant to the consideration of patentability in the case of the type of subject matter presently being claimed. The fact remains that Fountain et al do not disclose each and every aspect of the steps involved in the instantly claimed process and, consequently, the instantly claimed invention is patentable over Fountain, regardless of whether Fountain discloses all of the actual chemical components to be used in carrying out the instantly claimed process.

The rejection of claims 38, 49 and 58-60 under 35 USC §102(b) as being anticipated by Bölin et al. has been maintained. Withdrawal of claim 38 altogether and amendment of claim 49 (and hence claims 58-60) herein render moot this rejection. Applicants have made this amendment in the interest of expediting prosecution of the application; said amendment is not an acknowledgment of the validity of the Examiner's basis for rejection.

The rejection of claims 38, 49 and 58-60 under 35 USC §102(b) as being anticipated by U.S. Patent No. 5,629,001 to Michael et al. has been maintained. Again, in the interest of expediting prosecution of the application, claim 38 has been withdrawn from further prosecution in this application. Applicants reserve the right to resume prosecution thereof in a continuation application. Claim 49, and hence claims 58-60 dependent therefrom, have been amended herein so that they no

longer depend from withdrawn claim 38, thus rendering moot their rejection. It should also be pointed out that, as appropriate, all other claims dependent from claim 38 have been amended herein.

Claims 1-10, 19-22, 24, 25, 37, 38, 45-49 and 53-60 have been rejected as being indefinite. The Examiner has rejected claim 1 because the claim recites additional components introduced by a "wherein" bridge that are not actually recited in the step in which they are to be added. Although Applicants have not implemented the Examiner's specific suggestions, they have amended the claim herein to recite the stabilizing agents in step (a) and to make clear the nature of the inclusion of the stabilizing agents. Support for the language added can be found on page 10, lines 6-19 of the specification. The rejection of all other cited claims, ultimately dependent from claim 1, is moot in light of the amendment of claim 1.

Further with respect to this rejection of claim 1, Applicants note that the claim, prior to Applicants' April 5, 2001 Amendment, recited inclusion of a **single** stabilizing agent whereas the claim presently under rejection recites the provision of **one or more** stabilizing agents. There is nothing in the presently rejected language that would make this claim any more liable to the current ground of rejection than the previous version of the claim, and it is not understood how this could suddenly be made an issue by the Examiner.

Certainly, the Examiner's statement that the April 5, 2001 Amendment necessitated the new ground(s) of rejection and thus warranted the issuing of a final Office Action is inappropriate; it is respectfully requested that the finality of the rejection be withdrawn.

Claims 19-22, 37, 38, 45-49 and 53-60 have been rejected for reciting the phrase "liquid phase (X)." Although Applicants have not adopted the specific suggestions made by the Examiner, they have amended claims 19 and 20 herein to address the issue raised and, in general, to more clearly recite the subject matter regarded as the invention. In light of the amendments herein, no issue can be raised regarding lack of antecedent basis. Support for these amendments can be found in the passage running from page 10, line 26 through page 11, line 18 of the specification.

Claim 24 has been rejected for reciting the phrase "wherein step (b) comprises a fluid gas technique." The claim has been amended herein to clarify the limitation relative to the base claim. The amendment of claim 24 renders moot the rejection of claim 25. Although the Examiner did not raise the issue with respect to claim 23, in the interest of completeness Applicants have amended herein claim 23 essentially in the same way as they have amended claim 24 to avoid the possible raising of an issue at a later point in prosecution.

Claim 58 has been rejected essentially for reciting a vaccine composition without reciting the purpose of the vaccine; again, the Examiner has lost sight of the actual invention being claimed. Claim 58 does not recite a vaccine per se. It recites a composition comprising the vaccine delivery system of claim 49, which system ultimately is produced by the process of claim 1. As set forth earlier in this response, any water-insoluble antigen can potentially be used in this delivery system and thus it is inappropriate to require recitation of specific antigens. To further clarify this point for the Examiner, the preamble of claim 58 has been amended herein by deletion of the word "vaccine."

Claims 59 and 60 have been rejected as being incomplete for omitting essential elements and hence being indefinite. It should be pointed out that these claims, unlike other claims rejected by the Examiner, are directed to methods of treatment and, specifically, the prevention and treatment of *Helicobacter* infection. Accordingly, these claims have been amended herein to recite that the antigen is a *Helicobacter* antigen, as appropriate. Also, as with claim 58, the word "vaccine" modifying the word "composition" has been deleted. The further rejection of claims 59 and 60 for reciting the phrase "an effective amount" has also been addressed by the addition of the language specifying that the antigen is from *Helicobacter*.

The Examiner also asserts that the meaning of the word "treatment" in claim 59 is unclear. It is Applicants' contention that the juxtaposition of "treatment" in claim 59 with "preventing or reducing the risk of... infection" in claim 60 makes clear the meaning of the former term. Nonetheless, in the interest of expediting prosecution of the application, Applicants have added language to claim 59 to eliminate any doubt from the Examiner's mind.

Claims 1, 3-6, 9, 12, 19, 20, 23-25, 32-38, 45-49 and 58 stand newly rejected under 35 USC §102(b) as being anticipated by International Publication No. WO 96/36317. As indicated in the instant specification, and contrary to the Examiner's assessment, this reference does not disclose mixing an aqueous phase with a water-insoluble protein. Nothing is said about such active agents in the disclosure cited by the Examiner. In the passage particularly referred to by the Examiner, page 21, lines 10 and 11, reference is made to "certain hydrophobic drugs such as steroids," a class of compounds that does not even include proteins, let alone, more specifically, water-insoluble protein antigens. Thus, the cited reference cannot be said to anticipate all of the features of the present invention, and the rejection should be withdrawn.

Similarly, International Publication Nos. WO 95/11009 and 95/11010, also cited against the instant invention, are ineffective as anticipatory references. Again, the Examiner asserts that these references disclose mixing an aqueous phase

with a water-insoluble protein and, again, the assessment is in error. Neither of these references disclose the water-insoluble protein component of the instant invention. The Examiner apparently feels that disclosures such as that cited in WO 95/11009 that active agents include "... antigens, ... enzymes, and so on" is a teaching encompassing the water-insoluble antigens of the present invention. However, this is clearly inappropriate; the limitations of the present invention, as recited in the claims, are such that it begs the question, to say the least, to assert that the prior art teaches the active components of said invention. Furthermore, as indicated before, in light of the knowledge in the field at the time of the present invention, one of skill in the art would not have thought it possible to use the antigens in question in the context of the present invention and hence would not have interpreted the cited prior art teaching as including the use of the instantly claimed antigens.

Claims 1 and 26-31 stand newly rejected under 35 USC §103(a) as being obvious over International Publication No. WO 96/38475 of Bölin et al. in light of disclosure of Rabinovich et al incorporated therein by reference and in view of International Publication No. WO 96/36317. As the Examiner acknowledges, Bölin et al. fail to define all of the steps of the instantly claimed method, even taking into account the Rabinovich disclosure incorporated by reference. The Examiner

asserts that 96/36317 makes up for the deficiencies of the primary reference.

However, Applicants again refer to the discussion above of what this secondary reference teaches and the fallacy in the Examiner's assessment thereof. This secondary reference does not teach water-insoluble antigens in the context of W/O emulsion technology; again, the belief in the field at the time was that the two components are incompatible. The general teaching of Bölin linking a *Helicobacter* protein with polymer particles does not address this bias in the art. Thus, nothing in the combination of the cited references would even meet the "obvious to try" standard, let alone the more compelling, as determined in U.S. case law, "obvious to do" standard.

Claims 1, 15 and 16 have been rejected under 35 USC §103(a) as being obvious over International Publication No. WO 96/36317 in view of U.S. Patent No. 6,309,623 to Weers et al. Just as the Examiner refers to her earlier assessment of the primary reference, Applicants wish to refer to their assessment above of the same reference. Again, it cannot be said that the primary reference teaches water-insoluble protein antigens. Weers et al. is said by the Examiner to teach the utilization of a cationic surfactant and that this makes up for the gap in the teaching of the primary reference. However, the primary reference certainly does not teach the instant active agent and the Weers et al. teaching of a

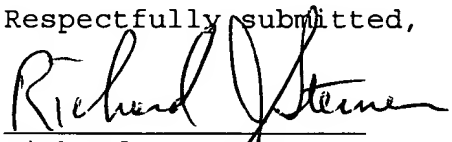
cationic surfactant certainly does not make up for this deficiency.

In view of the amendments and arguments set forth herein the claims are enabled, definite and free of the cited prior art. Reconsideration and allowance of pending claims 1-37 and 45-60 are respectfully requested.

The Assistant Commissioner is hereby authorized to charge any fees which may be due for any reason to Deposit Account No. 23-1703.

Dated: October 2, 2002

Respectfully submitted,



Richard J. Sterner
Reg. No. 35,372
Applicants' Agent
(212) 819-8783

Customer No.: 07470
(212) 819-8200

Enclosure

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A method for producing a vaccine delivery system comprising a plurality of polymer particles, wherein a water insoluble protein antigen is incorporated with the polymer particles, the polymer particles comprising a matrix polymer, wherein the method comprises:

(a) mixing an aqueous phase (W) comprising the water insoluble protein and one or more solubilizing agents with an organic phase (O) that comprises the matrix polymer in an organic solvent and is immiscible with W, to produce a W/O emulsion, wherein either W or O or both further comprise one or more stabilizing agents added prior to mixing to stabilize the W/O emulsion in the presence of the solubilizing agent(s) and promote the incorporation of the water insoluble protein within the polymer particles during step (b); and [the O phase comprisng the matrix polymer in an organic solvent;]

(b) forming droplets of said W/O emulsion by dispersing the emulsion in a fluid medium, and removing said solvent from the O phase of the W/O emulsion droplets to thereby form the polymer particles incorporating the water insoluble protein antigen[; and wherein in step (a) one or more stabilizing agents are provided in the W/O emulsion to stabilize the W/O emulsion in the presence of the solubilizing agent and promote the incorporation of the water insoluble protein within the polymer particles during step (b)].

16. (Twice Amended) The method of claim 12, wherein the hydrophilic surfactant is a zwitterionic surfactant selected from the group consisting of [(]3-1-propanesulphonate[)] (CHAPS), [(]3-[(3-cholamidopropy1)-dimethylammonio]-2-hydroxy-1-propanesulphonate[)] (CHAPSO), [(]N,N-*bis*-cholamide[)] (BIGCHAP), [(]N,N-bis-deoxycholamide[)] (deoxy BIGCHAP), lyso phosphatidylcholine, alkylbetaines and sulphobetaines.

18. (Twice Amended) The method of claim 17, wherein the one or more chaotropic agents is/are selected from the group consisting of a perchlorate, thiocyanate, guanidine, chlorate, iodide, bromide, nitrate and urea.

19. (Twice Amended) The method of claim 1[, wherein the method is] which includes a Double Emulsion (W/O/X) Solvent Evaporation Technique [and in step(b)] wherein the fluid medium in which the stabilized W/O emulsion is dispersed in step (b) is a liquid phase (X) which is immiscible with the O phase [to produce], said method producing a W/O/X double emulsion comprising W/O droplets from which the solvent is evaporated.

20. (Twice Amended) The method of claim 1[, wherein the method is] which includes a Double Emulsion (W/O/X) Solvent Extraction Technique [and in step (b)] wherein the fluid medium in which the stabilized W/O emulsion is dispersed in step (b) is a liquid phase (X) which is immiscible with the O phase [to produce], said method producing a W/O/X double emulsion comprising W/O droplets, and wherein the removal of the

organic [X phase extracts said] solvent from the O phase of the droplets is achieved through extraction by the X phase.

23. (Twice Amended) The method of claim 1, wherein the [method is] dispersal of the stabilized W/O emulsion in a fluid medium during polymer formulation in step (b) is achieved with a spray drying technique, [and in step (b)} wherein the stabilized W/O emulsion is dispersed in a gaseous medium to form a spray of W/O emulsion droplets from which said solvent evaporates.

24. (Twice Amended) The method of claim 1, wherein the dispersal of the stabilized W/O emulsion in a fluid medium during polymer particle formulation in step (b) [comprises] is achieved with a fluid gas technique [to form the polymer particles].

32. (Twice Amended) The method of claim 1, wherein the matrix polymer is a homo-or co-polymer selected from one or more of the group consisting of polyesters, polyanhydrides, polyorthoesters, polycarbonates, polyamides, poly(amino acids), polyacetals, polycyanoacrylates, polyacrylates, biodegradable polyurethanes, [non-erodable] non-erodible polyurethanes, polymers of ethylene-vinyl acetate, acyl substituted cellulose acetates, polysaccharides, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonated polyolefins, polyethylene oxide, polyethers and polyoxalates.

37. (Twice Amended) A vaccine delivery system produced by the method of claim 1, wherein the one or more stabilizing agents is/are a polymer selected from the group consisting of poly(vinyl pyrrolidone), poly(vinyl alcohol), polysaccharides, polyethyleneoxide and water soluble proteins, and wherein the method [is] includes a Double Emulsion (W/O/X) Solvent Evaporation Technique[and in step (b)] wherein the fluid medium in which the stabilized W/O emulsion is dispersed in step (b) is a liquid phase (X) which is immiscible with the O phase [to produce], said method producing a ~~W/O/X~~ double emulsion comprising W/O droplets from which the solvent is evaporated.

45. (Twice Amended) The vaccine delivery system of claim [38]37, wherein the matrix polymer is a homo- or co-polymer selected from one or more of the group consisting of polyesters, polyanhydrides, polyorthoesters, polycarbonates, polyamides, poly(amino acids), polyacetals, polycyanoacrylates, polyacrylates, biodegradable polyurethanes, [non-erodable] non-erodible polyurethanes, polymers of ethylene-vinyl acetate, acyl substituted cellulose acetates, polysaccharides, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonated polyolefins, polyethylene oxide, polyethers and polyoxalates.

49. (Twice Amended) The vaccine delivery system of any one of claims 37[, 38]and 45-48, wherein the polymer particles have an

average diameter of 0.05-20 μm according to the volume size distribution.

50. (Twice Amended) A [vaccine] composition comprising the vaccine delivery system of any one of claims 37[, 38] and [45-49] 45-48.

51. (Twice Amended) A method for the treatment of existing *Helicobacter* infection in a mammalian host, comprising administering to the mammalian host an effective amount of the [vaccine] composition according to claim 50 wherein the water insoluble protein antigen is a *Helicobacter* antigen.

52. (Twice Amended) A method for preventing or reducing the risk of *Helicobacter* infection in a mammalian host, comprising administering to the mammalian host an effective amount of the [vaccine] composition according to claim 50 wherein the water insoluble protein antigen is a *Helicobacter* antigen.

58. (Amended) A [vaccine] composition comprising the vaccine delivery system of claim 49.

59. (Amended) A method for the treatment of existing *Helicobacter* infection in a mammalian host comprising administering to the mammalian host an effective amount of the [vaccine] composition according to claim 58 wherein the water insoluble protein antigen is a *Helicobacter* antigen.

60. (Amended) A method for preventing or reducing the risk of *Helicobacter* infection in a mammalian host, comprising administering to the mammalian host an effective amount of the [vaccine] composition according to claim 58 wherein the water insoluble protein antigen is a *Helicobacter* antigen.